

**WHAT IS CLAIMED IS:**

1           **1.**       A method for identifying a therapeutic agent for use in treating a  
2   CAR-mediated disorder or condition, the method comprising:

3                        identifying a candidate therapeutic agent by screening one or more  
4   compounds to determine whether said compounds can modulate a CAR-mediated  
5   intermolecular interaction;

6                        administering the candidate therapeutic agent to a test mammal; and  
7                        determining whether the level of a cholesterol indicator is modulated in  
8   said test mammal.

1           **2.**       The method of claim 1, wherein said candidate therapeutic agent is  
2   5 $\beta$ -pregnan-3,20-dione.

1           **3.**       The method of claim 1, wherein said CAR-mediated disorder or  
2   condition is selected from the group consisting of: hypercholesterolemia, lipid disorders,  
3   atherosclerosis, and cardiovascular disorders.

1           **4.**       The method of claim 1, wherein the mammal is a cholesterol-  
2   elevated mammal.

1           **5.**       The method of claim 4, wherein the test mammal has a disruption  
2   in both CAR alleles.

1           **6.**       The method of claim 1, wherein said cholesterol indicator is the  
2   level of serum cholesterol.

1           **7.**       The method of claim 1, wherein said cholesterol indicator is the  
2   level of a member selected from the group consisting of HDL cholesterol, LDL  
3   cholesterol, and VLDL cholesterol.

1           **8.**       The method of claim 1, wherein said cholesterol indicator is the  
2   mRNA level of a gene involved in the regulation of cholesterol levels.

1           **9.**       The method of claim 1, wherein said CAR-mediated intermolecular  
2   interaction is CAR-mediated gene expression.

1                           **11.**    The method of claim **10**, wherein said candidate therapeutic agent  
2    is 5 $\beta$ -pregnan-3,20-dione.

1                           **12.**       The method of claim **10**, wherein said DNA binding domain is  
2 substantially identical to a DNA binding domain from a polypeptide selected from the  
3 group consisting of: CAR, a GAL4 transcription factor, an estrogen receptor, a  
4 progesterone receptor, a glucocorticoid receptor, an androgen receptor, a mineralcorticoid  
5 receptor, a vitamin D receptor, a retinoid receptor, and a thyroid hormone receptor.

1                           **13.**       The method of claim **12**, wherein said DNA binding domain is a  
2    CAR DNA binding domain and the response element is a CAR response element.

1                   **15.**       The method of claim **10**, wherein said reporter gene encodes a  
2 marker protein selected from the group consisting of: luciferase, alkaline phosphatase,  
3 beta-galactosidase, chloramphenicol acetyltransferase and green fluorescent protein.

1                   **16.**       The method of claim **1**, wherein said CAR-mediated intermolecular  
2 interaction is the binding of a polypeptide that comprises a CAR ligand binding domain to  
3 a ligand for CAR.

1                   **17.**       The method of claim **16**, wherein said polypeptide is a CAR $\alpha$  or a  
2 CAR $\beta$ .

1                   **18.**       The method of claim **16**, wherein said ligand for CAR comprises a  
2 sensor peptide.

1                   **19.**       The method of claim **18**, wherein said ligand for CAR comprises a  
2 receptor binding domain of a coactivator or a corepressor.

1                   **20.**       The method of claim **19**, wherein said coactivator is SRC-1.

1                   **21.**       The method of claim **20**, wherein said sensor peptide is rhodamine  
2 labeled ILRKLLQE.

1                   **22.**       The method of claim **16**, wherein the binding of the polypeptide  
2 that comprises a CAR ligand binding domain to the ligand for CAR is determined in the  
3 presence of a naturally occurring ligand for CAR.

1                   **23.**       The method of claim **22**, wherein said naturally occurring ligand  
2 for CAR is 5 $\beta$ -pregnan-3,20-dione.

1                   **24.**       The method of claim **16**, wherein said method comprises  
2 determining whether said compound can inhibit the interaction between the CAR ligand  
3 binding domain and the CAR ligand.

1                   **25.**       The method of claim **24**, wherein said CAR ligand is labeled.

1                   **26.**       The method of claim **25**, wherein said CAR ligand is radiolabeled.

1                           **27.**    The method of claim **24**, wherein said CAR ligand is labeled with a  
2                            fluorophore.

1                           **28.**    The method of claim 27, wherein said method comprises a  
2    fluorescence polarization assay.

1                           **29.**    The method of claim 27, wherein said method comprises a  
2                            fluorescence resonance energy transfer assay.

3  $5\alpha$ -androst-16-en-3 $\alpha$ -ol,  $5\alpha$ -androst-16-en-3 $\alpha$ -ol acetate,  $5\alpha$ -androstane-  
4 3 $\alpha$ -ol,  $5\alpha$ -androst-16-en-3 $\alpha$ -ol acetate and  $5\beta$ -pregnan-3,20-dione.

1                   33. A method for identifying a therapeutic agent for use in treating a  
2 CAR-mediated disorder or condition the method comprising:  
3                   administering a compound to a CAR compromised mammal; and  
4                   determining whether administration of the compound results in a change in  
5 cholesterol level compared to a mammal to which the compound is not administered.

1                           **35.**       The method of claim 33, wherein said cholesterol level indicator is  
2       the level of serum cholesterol.

1                   **36.**    The method of claim **33**, wherein said cholesterol level indicator is  
2 the level of a member selected from the group consisting of HDL cholesterol, LDL  
3 cholesterol, and VLDL cholesterol.

1                   **37.**    The method of claim **33**, wherein said cholesterol level indicator is  
2 the mRNA level of a gene involved in the regulation of cholesterol levels.

1                   **38.**    The method of claim **33**, wherein said CAR compromised mammal  
2 is a mammal having a disruption in both CAR alleles.

1                   **39.**    The method of claim **38**, wherein said CAR compromised mammal  
2 is a mouse.

1                   **40.**    The method of claim **38**, wherein said disruption occurs in the  
2 coding region for the DNA binding domain of CAR.

1                   **41.**    The method of claim **38**, wherein said disruption in a CAR allele  
2 comprises an insertion at codons for amino acid positions from about amino acid 21 to  
3 about amino acid 86 of CAR $\beta$ .

1                   **42.**    A method for treating a CAR-mediated disorder or condition, the  
2 method comprising:

3                   administering to a mammal having a CAR-mediated disorder or condition  
4 an effective amount of a therapeutic agent that modulates CAR-mediated regulation of  
5 cholesterol levels.

1                   **43.**    The method of claim **42**, wherein said therapeutic agent is  
2 identified by:

3                   screening one or more compounds to determine whether said compounds  
4 can modulate a CAR-mediated intermolecular interaction;

5                   administering the candidate therapeutic agent to a test mammal; and  
6                   determining whether the level of a cholesterol indicator is affected in said  
7 test mammal.

1                   **44.**       The method of claim **42**, wherein said CAR-mediated disorder or  
2 condition is selected from the group consisting of: hypercholesterolemia, lipid disorders,  
3 atherosclerosis, and cardiovascular disorders.

1                   **45.**       A non-human mammal having a genome that comprises a  
2 disruption in at least one CAR allele.

1                   **46.**       The non-human mammal of claim **45**, wherein said disruption  
2 comprises an insertion, deletion or mutation in a region of the CAR allele that encodes for  
3 a DNA binding domain of CAR.

1                   **47.**       The non-human mammal of claim **46**, wherein said disruption  
2 comprises an insertion at codons for amino acid positions from 21 to about 86 of CAR $\beta$ .

1                   **48.**       A non-human mammal having a genome that comprises a  
2 disruption in both CAR alleles.

1                   **49.**       The non-human mammal of claim **48**, wherein said disruption  
2 comprises an insertion, deletion or mutation in a region of the CAR allele that encodes for  
3 a DNA binding domain of CAR.

1                   **50.**       The non-human mammal of claim **48**, wherein said disruption  
2 comprises an insertion at codons for amino acid positions from 21 to about 86 of CAR $\beta$ .

1                   **51.**       The non-human mammal of claim **48**, wherein said non-human  
2 mammal exhibits an increased level of serum cholesterol relative to a wild-type mammal.

1                   **52.**       A method for producing a transgenic non-human mammal having a  
2 genome that comprises a disrupted CAR allele, the method comprising:  
3                   introducing into embryonic stem cells a polynucleotide that comprises a  
4 coding region for a portion of a CAR polypeptide, wherein the polynucleotide sequence  
5 includes a disruption in the coding region of a portion of said CAR polypeptide;  
6                   identifying a cell into which said polynucleotide sequence has been  
7 integrated into an endogenous CAR allele;

8 introducing said cell into a blastocyst, thereby forming a transgenic  
9 blastocyst;

10 implanting said transgenic blastocyst into a pseudopregnant mammal and  
11 allowing said pseudopregnant mammal give birth to a transgenic mammal.

1                   **53.**    The method of claim **52**, wherein said transgenic mammal contains  
2 a disrupted CAR allele in its germline.

1                   **54.**    The method of claim **53**, further comprising breeding said  
2 transgenic mammal to generate a heterozygous mammal comprising a disrupted CAR  
3 allele.

1                   **55.**    The method of claim **53**, further comprising mating a male and a  
2 female mammal each heterozygous for said disrupted CAR allele, to form progeny that  
3 are homozygous for said disrupted CAR allele.

1                   **56.**    The method of claim **52**, wherein said disrupted CAR allele  
2 comprises an insertion into a region of the CAR allele that codes for a DNA binding  
3 domain of CAR.

1                   **57.**    The method of claim **52**, wherein said disrupted CAR allele  
2 comprises an insertion at codons for amino acid positions from about 21 to about 86 of  
3 CAR $\beta$ .

1                   **58.**    The method of claim **56**, wherein said insertion comprises a  
2 selectable marker gene.

1                   **59.**    The method of claim **58**, wherein said marker gene encodes for  
2 neomycin resistance.